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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,646	08/02/2001	Shinichi Ayabe	JKM-001	5225

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KUBOVCIK & KUBOVCIK
SUITE 710
900 17TH STREET NW
WASHINGTON, DC 20006

EXAMINER	
KALLIS, RUSSELL	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,646	AYABE ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-46* is/are pending in the application.

4a) Of the above claim(s) *33,36,38,44 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-32,35,37,39-43 and 45* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 have been cancelled. Newly filed claims 25-46 are pending.

Newly submitted claims 33, 36, 38, 44 and 46 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 33 corresponds to a probe and reads upon non-elected Claim 9; and Claims 36, 38, 44 and 46 read upon non-elected Claims 17 and 18.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33, 36, 38, 44 and 46 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 25-32, 34-35, 37, 39-43 and 45 are examined. Claims 33, 36, 38, 44 and 46 are withdrawn.

Claim Objections

Claim 34 is objected to because of the following informalities: Claim 34 is dependent upon non-elected Claim 33. Appropriate correction is required.

Drawings

The drawings are objected to because figure 6 is missing or the drawings are misnumbered. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-28, 31-32, 35, 37, 40, 42-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The added claimed material which is not supported by the original disclosure is as follows: Newly added Claims 25-28 recite "an amino acid sequence having 55%, 70%, 80%, or 90% or more sequence identity to SEQ ID NO: 2" and newly added claims 31-32 recite "an isolated polynucleotide which has 80% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1" and "an isolated polynucleotide which has 90% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1" while the specification only supports "an isolated polynucleotide sequence having 50%, 70%, 80%, 90% or 95% or more sequence identity to SEQ ID NO: 1" and "an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1" and is silent with respect to percent homology or percent identity to SEQ ID NO: 2. Further, there is no support in the specification for any antisense DNA other than an antisense DNA of "an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1", and a DNA that hybridizes to SEQ ID NO: 1 (see Claims 4 and 6 as

originally filed and page 7 of the specification). Applicant is invited to point to the page and line number in the specification where support can be found. Absent of such support, Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 25-32, 35, 37, 40, 42-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant broadly claims an isolated polynucleotide encoding 2-hydroxyisoflavanone synthase with 55-90% sequence identity to SEQ ID NO: 2; an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; and an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2.

Applicant describes SEQ ID NO: 1 encoding SEQ ID NO: 2.

Applicant does not describe any other polynucleotide or amino acid sequence other than SEQ ID NO: 1 isolated from a legume or encoding an IFS of SEQ ID NO: 2.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43

USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicants fail to describe a representative number of polynucleotide sequences encoding a isoflavanone synthase protein falling within the scope of the claimed genus of polynucleotides: an isolated polynucleotide encoding polypeptides with 55-90% sequence identity to SEQ ID NO: 2, an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; and an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2.

Applicants only describe a single cDNA (SEQ ID NO: 1) and its corresponding amino acid sequence (SEQ ID NO: 2). Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for isoflavanone synthase protein activity, it remains unclear what features identify an isoflavanone synthase encoding polynucleotide. Since the genus of isoflavanone encoding polynucleotides has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Sequences encoding polypeptides with 55-90% sequence identity to SEQ ID NO: 2; sequences 70% identical to nucleotides 144-1712 of SEQ ID NO: 1 which encodes IFS from a legume; and an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2 encompass naturally occurring allelic variants,

isoflavanone synthase mutants, as well as sequences encoding proteins having no known IFS activity of which Applicant is not in possession. Accordingly, the specification fails to provide an adequate written description to support the genus of polynucleotides encompassed by the percent identity language or the substitution, deletion, addition and/or insertion language, as well as the derivative language as set forth in the claims. (See Written Description guidelines published in Federal Register/Vol. 66, No.4/Friday, January 5, 2001/Notices: p.1099-1111).

Applicant asserts in the response of 30 January, 2004 that the broadly claimed polynucleotides encoding the ISF proteins of the invention are easily identified by similarity to CYP93 class P450 enzymes, by testing for CYP93C activity, and by originating from a leguminous plant (response pages 11-15). This does not meet the requirements for written description as argued above.

Claims 25-32, 35, 37, 40, 42-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for plants transformed with SEQ ID NO: 1 or with polynucleotides encoding SEQ ID NO: 2 and host cells transformed with SEQ ID NO: 1 encoding SEQ ID NO: 2 wherein the host cells produces the IFS of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides encoding polypeptides with 55-90% sequence identity to SEQ ID NO: 2; plants or host cells transformed with an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; or an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2 wherein the product of IFS is altered in the transformed plant. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant broadly claims an isolated polynucleotide encoding 2-hydroxyisoflavanone synthase with 55-90% sequence identity to SEQ ID NO: 2; an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2; host cells transformed therewith and methods of producing 2-hydroxyisoflavanone synthase in cells; and plants transformed to have an increased or altered IFS product.

Applicant teaches screening a cDNA library with a probe of 422 bp (SEQ ID NO: 3), a fragment of a gene of unspecified function, from *Glycyrrhiza echinata* (Example 2 pages 23-24); transformation and expression in yeast using an expression vector comprising SEQ ID NO: 1 (Example 3 pages 25-26); testing for active 2-hydroxyisoflavanone synthase activity in isolates

from transformed yeast using a radiometric assay with radio-labeled liquiritigen and naringen (Example 4 pages 26-29); and transformation of tobacco with 2-hydroxyisoflavanone synthase cDNA (Example 7 pages 31-36).

Applicant does not teach isolation of any other sequences encoding an IFS of SEQ ID NO: 2 other than SEQ ID NO: 1; plants transformed with an IFS other than tobacco transformed with SEQ ID NO: 1; or altered IFS product levels in any plant transformed with a polynucleotide encoding any IFS of any sequence.

Isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40: 857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Further, the isolation of orthologous DNA sequences from other species introduces an element of unpredictability. The limitation is introduced in finding homologous regions that would adequately enable either PCR amplification or southern hybridization and would entail using either degenerate primers or probes with limited sequence identity. Thus the screen for

orthologous sequences would isolate many genes other than those of interest. The inherent unpredictability in isolation of a homologous sequence encoding the same protein activity is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun P. *et al.* Science Vol. 282; 13 November 1998, pp. 1315-1317; Abstract lines 4-6 and p. 1317 column 1, lines 37-56).

Based upon Applicant's limited guidance one cannot predict which embodiments would be operable and thus undue trial and error experimentation would be required by one of skill in the art to isolate and test the multitude of non-exemplified DNA sequences for IFS activity and transform and screen a myriad of non-exemplified transformed host cells from any species for non-exemplified recombinant 2-hydroxyisoflavanone synthase production and transform and screen a multitude of plants for non-exemplified altered levels of IFS reaction products encompassed by the claims.

Given the unpredictability in the art as to isolating DNA sequences that would encode an IFS protein; the breadth of the claims encompassing any plant or host cell transformed with an isolated polynucleotide which encodes any polypeptide having 55-90% sequence identity to SEQ ID NO: 1; any plant or host cell transformed with an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; or an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2; the lack of guidance in the

examples of the specification or in the prior art as to which nucleotide sequences, or portions or segments thereof, would either encode an IFS protein or would be required for IFS activity; and the undue trial and error experimentation required to practice the claimed invention, the invention is not enabled for the scope set forth in the claims.

Applicant's arguments filed 30 January, 2004 have been fully considered but they are not persuasive. Applicant asserts that all amino acid sequences belonging to CYP93C and having function as reported are IFS proteins (response page 14). It is not clear which sequences are being discussed and whether they were known in the art at the time of the effective filing date.

Applicant asserts that polypeptides having more than 55% sequence identity with SEQ ID NO: 2 are defined as originating from leguminous plants and as having IFS activity (response page 14). There is no evidence to support an IFS protein from a legume having at least 55% sequence identity to SEQ ID NO: 2.

Applicant asserts that that undue experimentation would not be required to confirm the function of a putative polynucleotide sequence as encoding an IFS protein (response page 16). Applicant's arguments are addressed above in the enablement rejection. Applicant's assertions are insufficient to overcome the literature and scientific reasoning cited by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Otani K. *et al.* Plant Physilogy, 1994, Vol. 105; pages 1427-1432.

The claims are broadly drawn to transformed or untransformed cells having a polynucleotide that encodes SEQ ID NO: 2 (a 2-hydroxyflavanone synthase from *Glycyyhiza echinata*) and any method for isolating the 2-hydroxyisoflavanone synthase from the cell.

Otani teaches cultured *Glycyyhiza echinata* cells and a method of extracting a crude enzyme sample that comprises the 2-hydroxyisoflavanone synthase from *Glycyyhiza echinata* (see Abstract and page 1428, the 2nd paragraph of column 1). Thus, the reference teaches all the limitations of Claims 39 and 41.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 25-32, 35, 37, 39-43 and 45 are rejected.

Claims 25-32, 34-35, 37, 40, 42-43 and 45 are deemed free of the prior art given the failure of the prior art to teach or reasonably suggest an isolated polynucleotide encoding a polypeptide with 55-90% sequence identity to SEQ ID NO: 2; an isolated polynucleotide which has 70% or more sequence identity to the nucleotide sequence of 144-1712 of SEQ ID NO: 1 and encodes IFS from a legume; an isolated polynucleotide that has at least 15 contiguous nucleotides of SEQ ID NO: 1 and codes for the amino acid sequence of SEQ ID NO: 2; an isolated polynucleotide sequence encoding an amino acid sequence shown as SEQ ID NO: 2 wherein one to 20 amino acids are substituted, deleted, added and/or inserted in the amino acid sequence shown as SEQ ID NO: 2; and plants and host cells transformed therewith.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russel Kallis Ph.D.
April 9, 2004

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638